Obstructive Sleep Apnea

Oral Appliance vs. Auto titrating Positive Airway Pressure

By

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CERTIFICATE OF APPROVAL

MASTER'S THESIS

This is to certify that the Master's thesis of

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has been approved by the Examining Committee for the thesis requirement for the Master of Science degree in Oral Biology at the June 2013 graduation.

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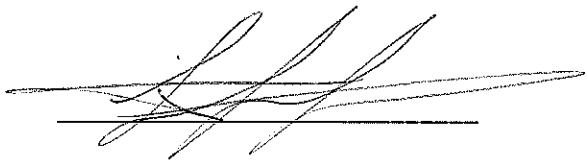

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ABSTRACT

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Oral Appliance vs. Auto titrating Positive Airway Pressure
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Introduction: Obstructive sleep apnea (OSA) is characterized by episodes of complete or partial upper airway collapse when breathing is periodically stopped (apnea) or markedly reduced (hypopnea). It is diagnosed in a sleep study by polysomnography (PSG) that determines an apnea-hypopnea-index (AHI). Positive airway pressure (PAP) is the most common approach for treating OSA. Oral appliances (OA) are sometimes used as primary therapy for OSA and for patients unable to tolerate PAP.

Objective: This prospective, randomized, cross-over controlled study compares the efficacy and compliance of the Thornton Adjustable Positioner (TAP-3) to auto titrating positive airway pressure (APAP) in the treatment of mild to moderate OSA (AHI>5<30).

Methods: 46 participants randomly assigned to TAP-3 or APAP undergo a 2-week device acclimation period, then, are titrated to optimal an AHI before the 4 week treatment phase. TAP-3 participants are titrated during a 2nd PSG while APAP records AHI while continuously adjusting pressure for optimal efficacy. These treatment AHI values will be compared to the AHI when OSA was diagnosed. Compliance is recorded for TAP-3 by an embedded electronic monitoring device (ibutton). After treatment sessions, compliance data is downloaded, the Epworth Sleepiness Scale is completed, and the Visual Analogue Scale (VAS) (appendix E) booklets to assess each night's sleep quality and the 1st device are collected. Participants then cross-over to the other device to complete a second 2 week acclimation and 4 week treatment phase. At study end the same data are collected, plus participants are asked

which device they preferred. Both devices are returned to participants and clinical use is based on consultation with their sleep physician.

Results: Protocol is being submitted for IRB review. Discussion: Previous studies comparing PAP and OA relied on subjective measures to assess OA compliance. This will be the first crossover trial that objectively measures both OA to PAP compliance.

Discussion/Conclusion: At present since we do not have any results to present, no conclusions can be made. Based upon published literature; the TAP appliance will show higher compliance and we will be able to directly compare the time the subjects used the TAP appliance and the time they used the APAP.

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LIST OF ABBREVIATIONS

AHI	……..	Apnea - Hypopnia Index
APAP	…….	Auto Titrating Positive Airway Pressure
CPAP	…….	Continuous Positive Airway Pressure
ESS	…….	Epworth Sleepiness Scale
OA	…….	Oral Appliance
OSA	…….	Obstructive Sleep Apnea
PAP	……..	Positive Airway Pressure
PSG	…….	Polysomnography
SE	……..	Sulcular Epithelium
TAP	…….	Thornton Adjustable Positioner
VAS	…….	Visual Analogue Scale

INTRODUCTION

The prevalence of OSA is estimated at 3 to 7% in the adult population, but that estimate may be low as it is derived from the treatment seeking population with a confirmed diagnosis of OSA. (Punjabi, 2008) If 5% of the 1.45 million active duty service members serving in the United States military have OSA, an estimated 72,500 military personnel may benefit from treatment. (DoD Perrsonnel & procruemennt statisitics, 2009)

Positive Airway Pressure (PAP) is the most common method of treating OSA, and this therapy is delivered by either continuous positive airway pressure (CPAP) or auto-titrating positive airway pressure (APAP) devices. Although PAP is highly effective at reducing AHI scores, several factors that affect APAP compliance also pose problems with its use in a military environment. All APAP machines must be connected to an electrical source to generate the appropriate air pressure. Tubing and masks must be cleaned and properly dried daily. Several component parts must be stored together and transported properly to prevent damage to the electronic unit. In addition to the challenges of maintaining the unit, patients often describe multiple adverse effects from using APAP including claustrophobia, poor fit, difficulty breathing, machine noise, airway dryness, congestion, and irritation. (Massie, 1999) The challenging environments to which some military members with mild to moderate OSA may be assigned may interfere with adequate usage and maintenance of APAP.

The TAP-3 oral appliance is small, lightweight and portable. It is free of electronics and does not require a power source. The materials to fabricate the appliance are inexpensive and repair of the appliance is simple. (Thornton, 2009) This study will directly compare APAP and the TAP-3 oral appliance may provide data on the suitability of the TAP-3 appliance as a treatment for mild to moderate OSA in military environments where APAP is not feasible. Such data might show that the TAP-3 appliance compared to a APAP may be more readily worn on a nightly basis by military members, and that the portability of a TAP-3 appliance may make it a cost effective, health enhancing option for military members in remote locations.

BACKGROUND AND SIGNIFICANCE

Obstructive sleep apnea (OSA) is a chronic condition characterized by frequent episodes of complete or partial upper airway collapse during sleep when for a period of time breathing is stopped or markedly reduced. These airway obstructions impair ventilation even while the neuromuscular respiratory effort remains intact, and results in decreased blood oxygen saturation and brief arousals from sleep. (AASM, 1999)

Loud snoring, poor sleep quality, daytime sleepiness and fatigue are hallmark signs of OSA (AASM, 1999) and are implicated in the pathogenesis of a variety of other conditions related to poor autonomic nervous system control. (Moyer, 2001) Cardiovascular disease, hypertension, stroke, abnormal glucose metabolism, neuromuscular conditions and cognitive impairment are common co-morbidities with OSA. (Moyer, 2001)

The prevalence of OSA is derived from treatment seeking populations where a diagnosis has been rendered. The estimated prevalence is 3 to 7% for adult men and 2 to 5% for adult women. (Punjabi, 2008) Besides male gender, other risk factors for OSA include obesity, ethnicity, age, craniofacial characteristics, and use of alcohol and tobacco. (Punjabi, 2008)

The diagnosis of OSA is traditionally made by overnight polysomnography whereby discrete episodes of apnea *(breathing stops)* and hypopnea *(breathing is shallower or slower than normal)* are measured per hour of sleep. These measures determine the apnea - hypopnea - index (AHI). (AASM, 1999) The addition of respiratory effort related arousals (RERA) - not necessarily related to apnea or hypopnea - to the AHI determines the respiratory disturbance index (RDI). (AASM, 1999) Classification of OSA disease severity is based on the number of sleep related obstructive breathing events per hour (AHI or RDI); 0 to 5 is normal, 5 to 15 is mild, 15 to 30 is moderate, and greater than 30 is severe. (AASM, 1999) However, the AHI may not be consistent from night to night in patients with mild OSA. Patients with moderate

and severe disease tend to show less night to night variation in AHI (Le Bon, 2000). Nightly variations in AHI are affected by numerous factors, including sleep position, diet, alcohol and medications. (McNicholas, 2008)

Surgery, positive airway pressure (PAP), either continuous (CPAP) or auto-titrating (APAP), and oral appliances (OA) are common treatments for OSA. Surgical therapies are numerous and varied and are all aimed at producing more air flow space. They range from nasal procedures, soft tissue reductions of the palate and pharynx, alterations of jaw and neck muscle attachments, and advancing the mandible and/or maxilla to enlarge the pharyngeal airway. (Franklin, 2009) (Elshaug, 2007) The success for these invasive procedures varies depending on procedure and outcome measures, but all are irreversible surgeries that are prone to significant morbidity. (Elshaug, 2007) (Lye, 2008)

Positive Airway Pressure

Traditionally, the most commonly accepted first line treatment for OSA has been CPAP whereby continuous positive airway pressure (at a constant force) keeps the airway open as a patient inhales during sleep. (Hoekema, 2004). To enhance CPAP compliance a variety of mask designs are available; nasal, oral, nasal/oral combinations, full face and full head. (Smith, 2004) Though the efficacy for reducing AHI or RDI to less than 5 events per hour by CPAP has been demonstrated, compliance - even with well fitting CPAP mask designs - is inconsistent and serves as a major therapeutic impediment for many patients. (Smith, 2004) Xerostomia, nasal congestion, rhinorrhea, headache, sneezing mucosal dryness of the upper airway and claustrophobia are other common side effects that reduce the use of CPAP. (Pepin, 1995) Patient compliance with CPAP ranges between 65% and 80% with 8 to 15% of patients refusing to accept treatment after a single night's use. (Waldhorn 1990; Krieger 1992) (Nino Murcia 1989;Waldhorn 1990; Rolfe 1991; Hoffstein 1992). Another study that measured CPAP compliance relative to a minimum standard of at least 4 hours per night for more than 70% of nights

showed compliance ranges from 46% to 85%. (Lewis 2004, Kribbs 1993, Pépin 1999) CPAP machines, including the associated hoses, masks and maintenance cost roughly between $500 and $2500 depending on the model, design and features.

More recently, APAP therapy has become increasingly attractive as a clinical option. It is the treatment of first choice at the new WRNMMC Sleep Disorder Clinic (the clinic name following the integration of Walter Reed and NNMC into WRNMMC). Rather than deliver a constant level of airway pressure as is provided by CPAP, an APAP device provides the minimum amount of pressure needed to maintain an unobstructed airway (Ayas,2004). This auto-tuning delivery of pressure is based on the ability of APAP devices to measure variability of airway resistance as a patient breathes. By providing a precise but variable pressure based on breath to breath feedback, APAP therapy modulates optimal pressure delivery as conditions change; as movement occurs during sleep, when someone is experiencing congestion from having a cold or allergies, or as someone is trying to fall asleep. The APAP technology also responds to body weight changes that can occur in with some OSA patients. The ability to make pressure adjustments enables APAP to avoid some of the possible compromises (greater potential for mask and mouth leaks and intolerance to constant pressure) associated with a higher fixed pressure of CPAP that may affect compliance. In a a randomized, crossover study, Wolfgang et al showed that there was a higher patient preference for the APAP due possibly for the APAP's ability to adjust pressure. (Galetke, 2008) Further, since pressure titration of a CPAP device is derived from an overnight sleep study, or sometimes a split night study, the established pressure setting may be less than optimal since sleep laboratories do not mimic a patient's home sleeping environment. (Morgenthaler, 2008)

APAP devices are the most common variation from CPAP devices for delivering PAP. In comparison studies, APAP matches CPAP in clinical outcomes and testing parameters (Stanley, 2012), (Galetke, 2008) such as sleep efficacy, and outcomes based on Epworth Sleepiness Scale (ESS)(appendix C),

Functional Outcomes of Sleep Questionnaire (FOSQ), Psychomotor Vigilance Task (PVT), *and* blood pressure (Kushida, 2011). In addition, a controlled parallel group study showed that APAP was equally effective to CPAP in lowering AHI while maintaining a lower air pressure values. (Damjanovic, 2009). By varying the pressure APAP devices may promote an increase in breathing synchrony not possible with CPAP and thus improve patient comfort and compliance. (Stanley, 2012) An additional advantage is that APAP device allows initiation of treatment without the need for an additional sleep study following OSA diagnosis; as is needed in order to set the pressure level for a CPAP device (Ayas, 2004). This ability to auto-titrate means APAP renders a valuable service for OSA patients who live far from sleep labs, and for whom, another sleep lab visit to titrate a CPAP might represent a hardship and a delay in treatment. Although initial cost of an APAP is greater than CPAP, the fact that a sleep study does not delay onset of APAP treatment (Hukins 2004; McArdle, 2010) renders the APAP cost effective. (McArdle, 2010). Both CPAP and APAP devices record information during their use that can be downloaded to a computer, but APAP devices record more variables, data that allows sleep physicians to perhaps better assess an OSA patient's treatment.

Oral Appliances

Oral Appliances (OAs) were introduced as a treatment for OSA in the 1980s and continue to be used both as a primary therapy and for patients unable to tolerate PAP. They function by moving the mandible, tongue and attached structures within the mouth and throat forward; thereby opening the airway space. (Hoekema, 2004) The appliances function on the same principle as that used in the jaw thrust maneuver of cardiopulmonary resuscitation (CPR) to open the airway. Research that supports the efficacy of oral appliances in the treatment of OSA suggests that they are less effective than PAP for reducing the AHI/RDI below 5 events per hour. (Pepin, 1995) However, several studies suggest greater compliance with OA than CPAP, though study results are variable and related to appliance design and

the follow-up protocol. (Ferguson, 2006) One such study (parallel design) showed that CPAP was used 4.4 nights per week and 4.2 hours per night whereas the OA was used 5.2 nights per week and 6.4 hours per night. OAs can produce side effects including dry mouth, jaw muscle soreness, and bite changes, but these effects are generally minimal and transient. (Ferguson, 2006)

Efforts to improve the efficacy of OA therapy have centered on varying how different appliances establish jaw protrusion. Most oral appliances for the treatment of obstructive sleep apnea are fabricated in a dental laboratory on custom stone models of the patient's upper and lower teeth that are attached to a dental articulator; a machine that reproduces the spatial relations between the maxilla and mandible. Laboratory fees for custom OAs can range from $100 to $400 while non-custom OAs, which do not involve dental laboratory fabrication, can be purchased over-the-counter for about $50.

The Thornton Adjustable Positioner (TAP-3) is an OA design approved by the Food and Drug Administration for the treatment of OSA. It is essentially two custom fit mouth guards (one for the top teeth and one for the bottom) with an attachment and adjustment mechanism that connects along the anterior portion of each mouth guard. This adjustable mechanism is set to advance the lower jaw until the airway space behind the tongue is open enough to alleviate symptoms of OSA. The TAP-3 appliance contributes to patient comfort because, unlike many OA designs, it allows some freedom for lateral movement of the mandible.

The laboratory fabricated TAP-3 appliance is made on stone models of the teeth. A bilaminate (hard top surface, soft bottom surface) thermoplastic acrylic sheet is heat softened and molded onto the teeth of the stone models. The TAP-3 hardware is then attached by auto-polymerizing dental acrylic resin, and then an additional thermoplastic sheet is heat softened and molded over the hardware. The appliance is then separated from the stone models, trimmed and polished for delivery. The TAP-3 appliance can be delivered to a patient in two short 20 minute visits; the first to make the impressions of the teeth and

the second to adjust the fit of the appliance. (Thornton, 2009) Typical laboratory fabrication time is 3 days, though hands-on construction time can be as fast as 6 hours. (Naval Postgraduate Dental School, 2009)

A chairside fabricated TAP-3 version is also available from the manufacturer. It uses heat softened plastic (Thermacryl) to line preformed shells that already contain the TAP-3 hardware. This chairside version of the TAP-3 is much bulkier than the lab fabricated custom appliance and therefore was not chosen for this protocol.

Numerous studies have demonstrated the efficacy and effectiveness of OAs in the treatment of OSA. (Hoekema, 2004) (Hoekema, 2008) (Hoekema, 2009) (Pancer, 1999) (Levandowski, 2007) However, only nine studies have directly compared PAP to OA, and all of these studies used CPAP. (Ferguson, 1996) (Ferguson, 1997) (Engleman, 2002) (Tan, 2002) (Barnes, 2004) (Hoekema, 2008) (Lam, 2007) (Randerath, 2002) (Clark, Glenn, 1996) Seven of the studies used a cross-over design and 2 studies used parallel designs. In all 9 studies, patient questionnaires or diaries were used to document compliance with the OA while compliance for CPAP was derived from electronic data that CPAP machines, by design, inherently record. These 9 studies showed variable amounts of compliance for OAs compared to CPAP, but no studies suggested greater compliance for CPAP than OA. In fact, most studies suggested OA superiority in terms of compliance. One of the 2 parallel design studies (OA vs CPAP) used the laboratory fabricated TAP-3 as the study device. APAP devices have not been directly compared to OAs.

The laboratory fabricated TAP-3 appliance has never been directly compared to CPAP or APAP in a cross-over randomized controlled trial. In the studies that have compared CPAP and OA patient compliance, OA compliance has never been electronically measured. In fact, our literature search found only one study that used an electronic monitoring device to determine the compliance of an OA for the treatment of sleep apnea. However, that study did not compare the OA to CPAP. (Lowe, 2000)

Thermochron iButtons

Thermochron iButtons (Maxim Integrated Products, Inc.) are small, encapsulated electronic devices that are used to track temperature over time for critical biologic situations such as transporting tissue and blood. They are also used to measure the ambient body temperature in live animal and human research. (DIRECTIVE 2002/95/EC OF THE EUROPEAN PARLIAMENT, 2003) (Maxim Integrated Products, Inc 2009) They can record distinct time and temperature data points at a specified interval (set by the user) that ranges from 1 to 255 minutes. Up to 2048 individual data stamps in the form of temperature values can be stored. The DS1921G model, which will be used in this study, has an additional 512 bytes of read/write nonvolatile (NV) memory. The data from the iButton can be downloaded directly to a computer via a USB port.

The DS1921G Thermochron iButton microchip and 3V lithium battery are contained within a stainless steel cylinder. The DS1921G is RoHS compliant, meaning that it conforms to the directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment commonly called the restriction of hazardous substances directive (RoHS). (DIRECTIVE 2002/95/EC OF THE EUROPEAN PARLIAMENT, 2003) RoHS compliance indicates that the device does not contain lead, cadmium, hexavalent chromium, mercury, polybrominated biphenyls (PBB), and polybrominated diphenyl ether (PBDE). (Maxim Integrated Products, Inc 2009) A search for the use of iButtons in the medical/dental literature revealed 5 articles where iButtons were used in or on a living subject. No literature was found where iButtons were used to monitor the compliance of a medical device. (Maxim Integrated Products, Inc 2009) (DIRECTIVE 2002/95/EC OF THE EUROPEAN PARLIAMENT, 2003) (Johns, 2009) (CPAP Supply USA, 2009) (Lindberg, 2006)

In this proposal the DS1921G Thermochron iButton will be embedded in acrylic and attached to the upper mouthguard of the TAP-3 to record intra-oral time and temperature over each 4 week study arm.

After consultation with Dr. Susan Runner, the Acting Division Director for the Center for Devices and Radiological Health Food and Drug Administration, a DS1921G Thermochron iButton was embedded in acrylic and attached to the TAP-3 for overnight use by the original principal investigator of this proposal, LCDR Kahn. In that preliminary trial the addition of the DS1921G to the TAP-3 was comfortable and the data it collected when downloaded onto a laptop clearly recorded time and temperature to show when the appliance was actually being used intraorally. This is the only known use of an iButton in a TAP-3 device.

LITERATURE REVIEW

Repeated literature searches used search terms that focused on OSA, OAs, CPAP, APAP and iButtons. The literature search provided the basis and support for the background and significance of obstructive sleep apnea, its epidemiology, pathophysiology, and various treatment modalities. Although numerous search results were found for many of the topics, generally one or two articles on the topics of OSA, OAs, CPAP, APAP and iButtons provided the foundation to support claims made in the background and significance. The remainder of the articles provided specific relevance for my study both in design and methodology.

As of March 2013, no cross-over controlled study had yet been published that directly compared an OA to either CPAP OR APAP using an electronic assessment of nighttime compliance.

MATERIALS AND METHODS

In this proposed study, 46 subjects will be treated with each therapy in two successive four week sessions utilizing a randomized cross-over study design. Daily/hourly usage will be measured by the electronic monitors within the APAP machines and the Thermochron iButton embedded within the TAP-3 appliance. Subjective changes in daytime sleepiness will be measured with the Epworth Sleepiness Scale. A Visual Analogue Scale for sleep quality with 0 representing worst sleep imaginable and 10 representing best sleep imaginable will be completed after each night's sleep. The null hypothesis is that there will be no difference

in efficacy and compliance between APAP and the TAP-3 oral appliance in the treatment of mild to moderate OSA. The data may provide an objective basis by which clinicians choose a treatment approach for mild to moderate OSA; especially if patients may be located in austere environments.

The subjects who consent to this proposal will experience no more risks than patients with mild to moderate OSA who are being treated by either APAP or OA; treatments that are both within the standard of care. Only human subject volunteers in a cross over design can provide the type of data that will clarify the questions of efficacy, compliance and preference concerning the use of APAP and OA. Subjects in this study will directly benefit by study participation because they will experience each therapy, be provided objective measures of AHI scores and compliance with each therapy, and have subjective data on their self-appraisals of therapy preference. After the study the subjects will keep and use the appliance of their choice in the continuing treatment of their OSA under the care of their physician. The risks for both interventions are generally considered minor and vary in frequency. (Hoekema, 2004) Although data suggest that OA therapy produces less change in AHI than CPAP or APAP therapy, this study could show that OA compliance may be superior to APAP, meaning that an OA compared to APAP may provide more nights and hours of OSA symptom improvement. Commonly reported minor and temporary side effects of OAs are temporomandibular joint (TMJ) pain, muscle pain, tooth pain, salivation, TMJ sounds, dry mouth, gum irritation, and morning-after occlusal changes. Severe and continuous side effects are rare and present as more intense aspects of the previously listed items. (Ferguson, 2006)

THE PLAN

Subject Population

Male and female military health care beneficiaries age 18 and older presenting with the diagnosis of mild to moderate obstructive sleep apnea as defined by an apnea/hypopnea index greater than 5 and less than or equal to 30.

Inclusion Criteria

1. Adult
2. AHI >5 but ≤30
3. Adequate dentition to retain an oral appliance as determined by dental examination

Exclusion Criteria

1. Age less than 18
2. AHI > 30
3. Edentulous or with dental disease that prevents oral appliance therapy (periodontal disease, tooth decay)
4. Inability to protrude mandible more than 5mm
5. Temporomandibular joint disorder (TMD)
6. Previous treatment of sleep apnea
7. Morphological airway abnormalities
8. Endocrine dysfunction
9. Severe cardiac or pulmonary disease
10. Patient's with diagnosed central sleep apnea
11. Any contraindications to CPAP therapy

Recruitment

At the Walter Reed National Military Medical Center (WRNMMC), patients suspected to have a sleep disorder are referred to the sleep lab for an evaluation that includes overnight polysomnography (PSG). This standard of care diagnostic approach is essential because less than 50% of patients with symptoms suggestive of sleep apnea actually have the diagnosis. (Hoekema, 2008). The AI (a sleep medicine physician) will inform the patient of the ongoing study and consent the patients to participate if they meet the

inclusion criteria after the completion of the sleep study.

Consent Process

At the appointment to initially evaluate OSA, the sleep medicine physician will ask the patient if they have interest in a study being conducted WRNMMC which compares a jaw appliance with an auto-titrating positive air pressure device in the treatment of OSA. To avoid any coercion, patients will be told that anyone diagnosed with mild to moderate sleep apnea and meets the dental requirements can participate in the study. If a patient is not interested in hearing about the study, they will still receive treatment at the WRNMMC sleep medicine clinic based on their diagnosis. If they express interest hearing about the study, then the AI will review the study and consent process.

A potential subject will be given as much time as needed to read the consent and HIPAA documents and ask questions in order to decide if they wish to be in this voluntary study. The AI will answer all questions and reiterate that participation is voluntary and that a subject can exit the study at any time and will still receive treatment. The AI will verbally review the following information, which will be in the Informed Consent document. The study will last 12 weeks consisting of two successive six week treatment sessions (the first 2 weeks of each are used for acclimation to each device) using one therapy and then the other therapy. Both treatments are accepted by the American Academy of Sleep Medicine. APAP therapy is currently considered the first line treatment for OSA at WRNMMC. OAs are currently considered second line therapy for patient's unable to use PAP (Ferguson, 2006) Patients will be told that the oral appliance is a TAP-3 that in this study is customized with an iButton

Figure 1. Example of **maxillary and mandibular TAP-3 appliances** with iButton attached to maxillary guard. Photograph by author.

thermometer about the size of nickel to record the temperature. The patients will be shown a photograph of the TAP-3 with the iButton in place. Patients will NOT be told that the thermometer is used for monitoring compliance as this might bias their usage. Randomization will determine which therapy will be started first. A description of the devices and procedures will be presented.

It will be explained that whether or not a patient consents to be in the study there is a 1 week waiting period before any therapy can be started. This 1week period exists because it takes 1 week to obtain the APAP device and/or fabricate the TAP-3 appliance. The enrolled patient will (based on the assigned treatment) will meet with a Durable Medical Equipment (DME) representative at the sleep center. The DME representative will deliver, fit, and adjust the APAP device to optimize comfort. Or, the subject will be seen in the Prosthodontics Department of the Naval Postgraduate Dental School have their custom TAP-3 appliances made and fitted.

Once the APAP and TAP-3 are ready for use, subjects will be instructed to use the assigned device (determined by randomization) for 2 weeks to build a certain comfort level with the selected device. After the 2 weeks period the subject will report back to the sleep center; subjects assigned with the TAP-3 appliance will receive a sleep study to titrate the TAP-3 by an overnight PSG. Subjects with the APAP will have the device inspected and the air pressure range narrowed. Titration is necessary for each device to determine the settings which maximize the reduction in AHI.

Four weeks following the titration PSG, subjects will return to the sleep lab and return the first device used. Electronic monitoring data from the first device will be collected.

Subjects will receive the second device and will have a 2 week period to adjust to it. After 2 weeks the subject will report back to the sleep center; subjects assigned with the TAP-3 appliance will receive a sleep study to titrate the TAP-3 by an overnight PSG. Subjects with the APAP will have the device inspected and the air pressure range narrowed based on the data collected from the device.

Subjects will return to the sleep lab following the second 4 week arm so that electronic monitoring data from the second device can be collected and to complete the study.

Subjects will also complete a 0 to 10 Visual Analogue Scale (VAS) for sleep quality after each night of sleep. The VAS will be scored whereby 0 means the worst sleep imaginable and 10 means the best sleep imaginable. The VAS for sleep quality will be collected after each 4 week treatment session. After each 4 week treatment session subjects will also complete the Epworth Sleepiness Scale which is a measure of daytime sleepiness. At the completion of the study subjects will be asked to declare which therapy they preferred.

Following the second 4 week treatment session subjects will be able to use either device. That decision will be based on their personal preference and the recommendations from their primary care physician or sleep medicine physician. As with all sleep medicine clinic patients, study subjects will have follow-up treatment at regular intervals by the staff at the WRNMMC sleep medicine clinic. For subjects who choose to use the oral appliance, maintenance will be monitored by their primary care dental provider (military or civilian).

Study Design

This is a prospective, randomized, crossover design trial that compares the efficacy and compliance between the TAP-3 oral appliance and APAP therapy for the treatment of mild to moderate obstructive sleep apnea. Subjects will be assigned to either therapeutic device first through use of a randomization table generated electronically from the website http://stattrek.com/Tables/Random.aspx before the study starts. Due to the obvious nature of the treatments, patients will not be blinded to their allocation.

Confounding variables including patient pre-conceptions, design features of the appliance, and medical co-morbidities will be addressed by randomization and the cross over design.

Study Procedures

1. Sleep center visit #1
    a) Patient present at sleep, clinical exam suggests OSA
    b) Patient appointed for a diagnostic PSG
    c) Patient informed of study at initial evaluation for OSA and appointed for polysomnograph
    d) Consent/ HIPAA will be completed, signed and a copy given to patient
    e) If patient is interested, he/she will be referred to the prosthodontics department
        i. If patient not interested, the patient will continue with normal procedure of the sleep center
2. Dental visit #1
    a) Dental exam
        i. If patient does not satisfy the dental inclusion criteria, the patient will be referred back to the sleep center to continue with normal procedure of the sleep center
    b) Alginate impressions – Diagnostic casts
    c) George gauge recording - patient must be protruding their lower jaw approximately 75% of maximum protrusion
3. Sleep center visit #2
    a) Patients complete an overnight diagnostic polysomnograph
    b) The PI (A sleep medicine physician) the patient and discuss their diagnosis
    c) If they fulfill the inclusion/exclusion criteria confirm intent to participate in study.
        i. If they don't exit and pursue APAP only
    d) Patient will be randomized to either APAP group or the TAP group
4. Assignment to TAP or APAP for the first 6 week treatment session using randomization table.
5. Patients that were randomly assigned to the TAP will be appointed 2 dental appointment and 1

sleep center appointment:

a) Dental appointment #2
    i. Adjust TAP-3 appliance to optimize fit and comfort
        1. TAP appliance will contain an acrylic button to hold place for the future i Button.
    ii. Verify approximately 75% maximal protrusion when maxillary attachment hook is at the midpoint of its advancement
    iii. Adjust appliance or add acrylic as needed to maintain normal bite and improve comfort
    iv. Patient will be given care instructions and instructed to wear the TAP for two weeks
b) Sleep center visit #3
    i. Overnight PSG
    ii. Adjust the TAP-3 using the allen wrench until AHI is reduced to less than or equal to 5 or the patient cannot tolerate further advancement
c) Dental appointment #3
    i. Make any necessary adjustments
    ii. Remove the acrylic button
    iii. Activate the iButton mission (20 minute intervals to collect time/temperature data) with a 24 hour delay, thus the study data will be recorded from the patient's home use.
    iv. Encapsulate the iButton - apply a thin coating of Vaseline to the iButton followed by a thin coat of clear dental acrylic resin to completely seal/encapsulate the iButton.
    v. Subjects given Visual Analogue Scale booklet for sleep quality and instructions for device maintenance

vi. Patient instructed to wear the TAP for four weeks

6. Patients that were randomly assigned to the APAP will be appointed for 2 appointments at the sleep center 1 final follow up visit. (appendix A)
    a) Sleep center appointment #1
        i. Patient receives APAP and given use and care instructions (Tricare approval process for APAP confirmed and patient will meet with Durable Medical Equipment (DME) representative.)
        ii. Patient instructed to use the appliance for two weeks
    b) Sleep center appointment #4
        i. APAP is checked for proper function
        ii. Based on computerized data; adjust the mask, air flow rate and pressure range to settings that provided the reduction in AHI to less than or equal to 5 or the patient cannot tolerate further increases in air flow
        iii. Subjects given Visual Analogue Scale booklet for sleep quality and instructions for device maintenance
        iv. Patient instructed to use the APAP for 4 weeks.
7. Final follow up visit
    a) 4-week follow up visit conducted by the PI and AI for compliance data and recovery
        i. Collect the devices used in the first arm
        ii. Remove the iButton and acrylic shell (if used during the first arm)
        iii. Download data from electronic monitoring device
        iv. Collect first session Visual Analogue Scales for sleep quality
        v. Complete Epworth Sleepiness Scale: Terms of use for the ESS can be found at http://epworthsleepinessscale.com/terms-of-use/ (Rolfe, 1991)

8. Deliver to the subjects the appliances for the second arm of the study and repeat steps 5-9
9. End of study follow up visit conducted by the AI
    a) Subjects will be asked to state which therapy they preferred.
    b) Subjects retain each device
10. Data Collection complete
11. Data Analysis

OA instructions

Subjects will be given their oral appliance at the start of the 6 week assessment (2 weeks of acclimation and 4 weeks of trial) with written instructions on how to use and maintain the appliance. (Airway Management Inc.) Subjects will be instructed to adjust the amount of protrusion until a comfortable position is found that also alleviates their symptoms. (Hoekema, 2008) Subjects will be given a log to record the adjustments to the device (appendix B). The goal is to maximize patient comfort in an effort to optimize compliance at as close to therapeutic effects as reasonably achievable. Patient self adjustment is in accordance with instructions as published by the manufacturer. Self adjustment is standard clinical procedure and is not unique to this study.

APAP instructions

Subjects will be given home instruction on the use and maintenance of their APAP machine by the Durable Medical Equipment (DME) representative. Pressure ranges will be determined by prescribing physician and will not be adjustable by the subject.

Data Collection

As each subject is enrolled they will be given a study ID number (1 to 46) based on the chronology of their enrollment. A master list, kept in a locked file in the AI's locked office will associate subject name, last four of their social security number, telephone number, email address and date of study enrollment with the

study ID number. Signed Informed Consent and HIPAA forms will be kept in a locked file in the AI's office. Each subject will be given a copy of the signed Informed Consent and HIPAA forms. Only the PI and AI will have access to the master list and it will only be checked for contact data in case a subject must be contacted due to scheduling problems or some new information is learned that a subject needs to know. The study ID number will identify each subject's individual study data file. These files will be stored in a locked cabinet in the PIs office and will hold a paper copy of the subject's individual data collection sheet, summary data collection sheet, the Visual Analogue Scale (VAS) (appendix E) booklet to assess sleep quality, the Epworth Sleepiness Score (ESS) (appendix C) inventory after each therapy, and post study question- Which therapy did you prefer? Each of these items will also be identified by the study ID number. Individual subject data collection sheets and a summary data sheet will also be maintained on the password protected desktop computer in the PI's locked office.

Baseline data from the initial diagnostic appointment before the start of the study; age, weight, gender, ESS score and the AHI score will be entered into the data collection sheet. Subsequently, AHI scores determined at the titration PSGs, ESS and VAS scores after each 4 week therapy session and the post study preference question answer will be entered into the data collection sheets. Compliance data will be recorded on the data collection sheets by electronically downloading the data from the APAP monitoring card and from the DS1921G Thermochron iButton that is retrieved from the OA. A laptop provided for this protocol by the WRNMMC IT department will be used for downloading the iButton compliance data. No other data will be entered onto the laptop.

The Epworth Sleepiness Scale assesses daytime sleepiness. It was introduced in 1991, is freely available online and has high specificity (100%) and sensitivity (93.5%). (32) (8) The iButton will be attached to the OA and set to record data points every 20 minutes for the 4 week trial duration. The data from the iButton will be downloaded to a computer and the total time wearing the device will be calculated to the nearest 20 minute interval.

Subject initiated contacts via phone or email to either the PI or AI with respect to adverse events, side effects or questions will be recorded on a log (appendix D). The log will contain the call date and time, the nature of the question and response as well as any ancillary information necessary to clarify the contact. The log will be maintained by the PI on a desktop computer located in a locked office.

RESULTS

At the time of writing this thesis, there are no results to report on. Military integration brought many changes and reorganization. Most importantly, we now have a state of the art sleep center. The protocol was adjusted to include procedures of the new sleep lab and the fact that APAP instead of the CPAP is the preferred treatment modality used at WRNMMC. The protocol will be submitted to the IRB in September 2013 when the study will be executed by sleep center and prosthodontics department staff due to its time sensitivity.

STATITICAL ANALYSIS

At this point there is not data available for analysis. However; this study will produce data that compares, in the same patients, objective time measures of APAP and OA use in the treatment OSA. It will also compare the diagnostic AHIs to AHIs for the 4 week treatment trials that are achieved by titration at the end of each device acclimation period.

Patient perception data on sleep quality for each night using a Visual Analogue Scale, on daytime sleepiness via the Epworth Scale, and device preference at study end will also be collected.

Statistical analysis will be completed by using the Mann-Whitney U test U test.

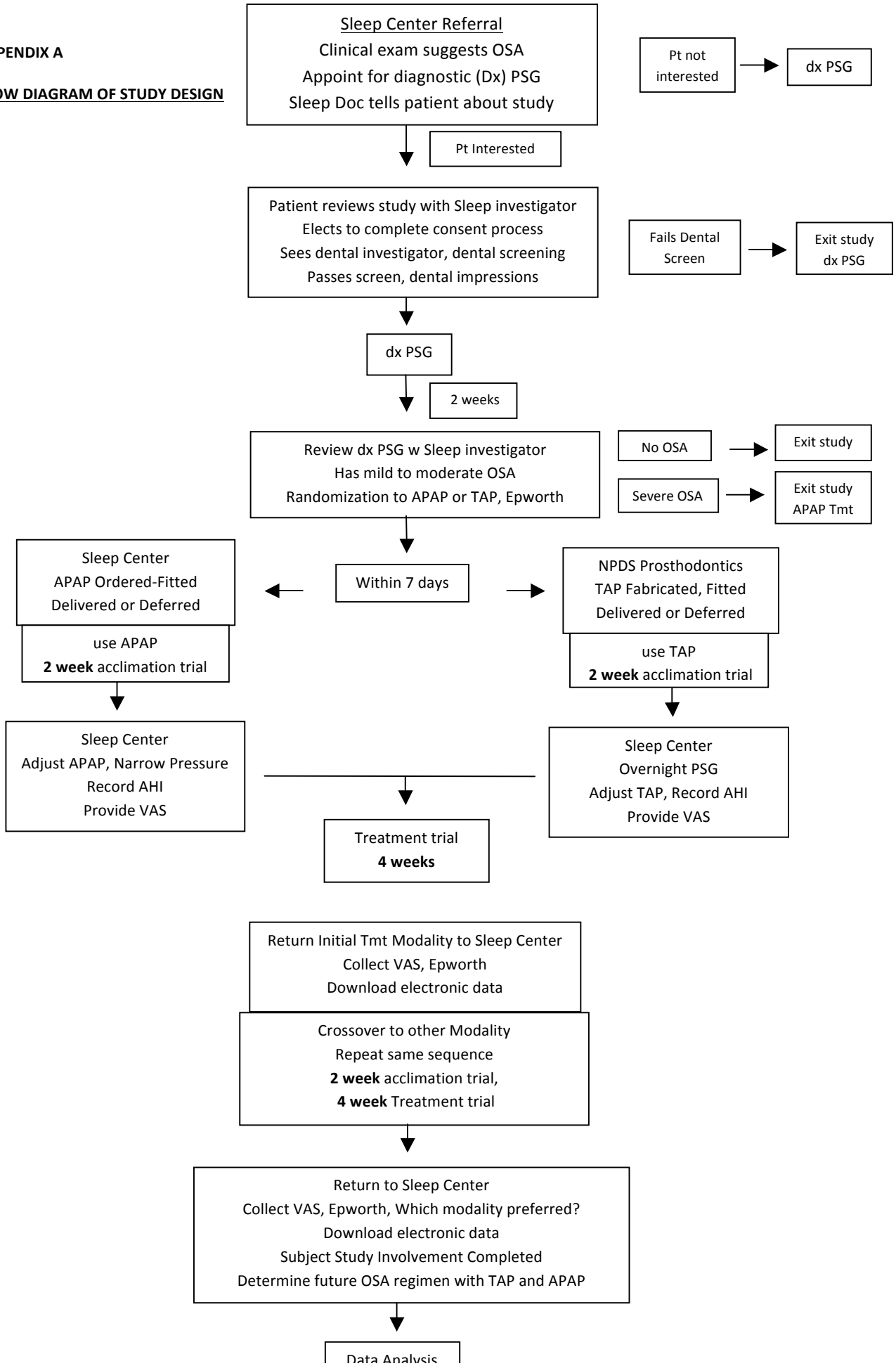
DISCUSSION/CONCLUSION

This is the first cross-over design study to objectively measure OA compliance in comparison to PAP compliance. The study will collect objective and subjective data that will provide, for each treatment, predictive benefit in terms of compliance and preference.

It is important to clarify that these objective data on compliance and AHI do not assess the effect of treatment on autonomic nervous system problems that lead to the onset of OSA (ANS). However, using values obtained from this study, future studies may develop a data set that could link objective compliance and AHI data to measures such as Heart Rate Variability to determine the effect of OSA treatment on the autonomic nervous system.

APPENDIX A

FLOW DIAGRAM OF STUDY DESIGN



APPENDIX B

Adjustment Log

Subject's Oral Appliance Adjustment Log	
Date/Time	Amount and Direction of adjustment

APPENDIX C

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* change of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Thank you for your cooperation

APPENDIX D

Phone Consultation Log

Date/time	Nature of question or comment	Response from PI or AI

APPENDIX E

Study ID # _____

Visual Analogue Scale for Sleep Quality

Please rate the quality of each night's sleep by making a mark on the 0 to 10 scale below.
0 represents worst sleep imaginable and 10 represents best sleep imaginable.
Please check which therapy you used or if you did not use a therapy.

Night 1

Worst Sleep Imaginable — Best Sleep Imaginable

0_____10

APAP _____ Oral Appliance _____ No appliance _____

Night 2

Worst Sleep Imaginable — Best Sleep Imaginable

0_____10

APAP _____ Oral Appliance _____ No appliance _____

Night 3

Worst Sleep Imaginable — Best Sleep Imaginable

0_____10

APAP _____ Oral Appliance _____ No appliance _____

Night 4

Worst Sleep Imaginable — Best Sleep Imaginable

0_____10

APAP _____ Oral Appliance _____ No appliance _____

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